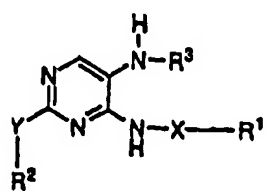
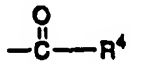
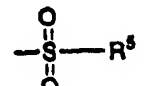
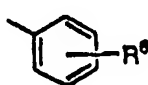




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<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(a)</p> </div> <div style="text-align: center;">  <p>(b)</p> </div> </div> <div style="text-align: center; margin-top: 20px;">  <p>(c)</p> </div>		
(57) Abstract <p>Novel 4,5-diamino pyrimidine derivatives having the inhibitory activity of cyclic guanosine 3',5'-monophosphate phosphodiesterase and tumor necrosis factor, physiologically acceptable salt, solvate or metabolically readily convertible ester thereof and a process for producing the same are described. The present compounds are represented as general formula (I) in which X is a direct bond, C₁₋₄ alkylene, C₁₋₄ alkyleneoxy, C₁₋₄ alkoxyphenyl or phenyl C₁₋₄ alkylene; Y is a direct bond or C₁₋₂ alkyl; R¹ is (i) 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, halogen, nitro, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy, (ii) C₄₋₁₀ carbocyclic compound or (iii) hydroxy C₁₋₄ alkoxy; R² is 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, hydroxy, halogen, nitro, hydroxy C₁₋₅ alkyl, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy; R³ is hydrogen, (a) or (b) in which R⁴ and R⁵ are each independently selected from a group consisting of hydroxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen C₂₋₆ alkenyl and C₁₋₄ alkoxy or R⁴ and R⁵ represent each independently (c) in which R⁶ is selected from a group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen, nitro and C₁₋₄ alkoxy.</p>		

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**4,5-DIAMINOPYRIMIDINE DERIVATIVES AND A METHOD
FOR THE PREPARATION THEREOF**

5 FIELD OF THE INVENTION

The present invention relates to novel 4,5-diaminopyrimidine derivatives useful in prevention or treatment of diseases implicated in respiratory system by inhibiting cyclic guanosine 3',5'-monophosphate phosphodiesterase. In addition, the present invention relates to a process for
10 producing the said compounds.

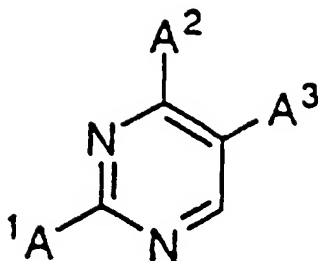
BACKGROUND OF THE INVENTION

15 It is known that cyclic guanosine 3',5'-monophosphate (cGMP) induces an relaxation of cardiac muscle or smooth muscle and is implicated in the cellular growth of lymphocyte. However, there are reports in which cGMP is converted into inactive 5'GMP by cGMP phosphodiesterase, so the action of cGMP is lost. Therefore, compounds having inhibitory activity of
20 cGMP phosphodiesterase will be able to maintain or increase level of cGMP and so will act as keeping a symmetrical metabolism. As such, the compounds can be effectively used in the prevention or treatment of hypertension, cardiagra, arteriosclerosis, respiratory system disease such as chronic bronchial asthma or bronchitis, etc.

25

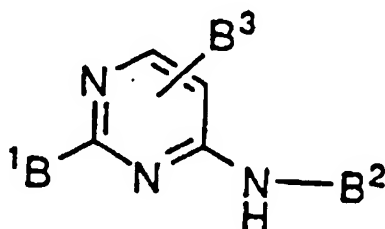
US Patent No. 5,318,975 describes, as inhibitor of cGMP phosphodiesterase, 5-aminopyrimidine derivatives compounds of the following formula A:

30



10 wherein A¹ represents hydrogen or imidazole substituted with lower alkyl, A² represents hydrogen or lower alkyl and A³ represents imidazolecarboxylamide substituted with lower alkyl.

EP 640,599 describes, as inhibitor of cGMP phosphodiesterase, 4-aminopyrimidine derivatives compound of the following formula B:

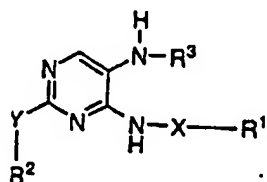


25 wherein B¹ represents 4-15 membered heterocyclic ring substituted with lower alkyl, lower alkoxy, halogen, etc., B² represents 4-15 membered heterocyclic ring substituted with lower alkyl, lower alkoxy, halogen, nitro, ester, etc. or hydroxy(lower alkoxy), B represents 4-15 membered heterocyclic ring substituted with lower alkyl, lower alkoxy, halogen, nitro, sulfone, etc.

DETAILED DESCRIPTION OF THE INVENTION

30 In one aspect, the present invention provides novel

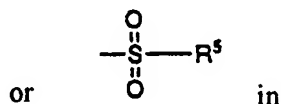
4,5-diaminopyrimidine derivatives or physiologically acceptable salts, solvates or metabolically readily convertible ester thereof which have the inhibitory activity of cGMP phosphodiesterase. The compounds are represented as the general formula (I):



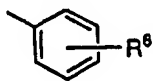
Formula I

in which X is a direct bond, C₁₋₄ alkylene, C₁₋₄ alkyleneoxy, C₁₋₄ alkoxyphenyl or phenyl C₁₋₄ alkylene; Y is a direct bond or C₁₋₂ alkyl; R¹ is (i) 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, halogen, nitro, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy, (ii) C₄₋₁₀ carbocyclic compound or (iii) hydroxy C₁₋₄ alkoxy; R² is 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, hydroxy, halogen, nitro, hydroxy C₁₋₅ alkyl, C₁₋₆ alkyl, C₃₋₆ alkenyl

and halogen C₁₋₄ alkoxy; R³ is hydrogen,



which R⁴ and R⁵ are each independently selected from a group consisting of hydroxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen C₂₋₆ alkenyl and C₁₋₄ alkoxy or R⁴ and R⁵ represent each independently

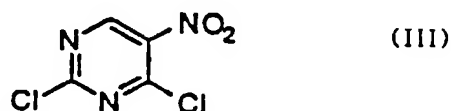


in which R⁶ is selected from a group consisting of hydrogen,

hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen, nitro and C₁₋₄alkoxy.

5 The compound of the general formula I may be in the form of optical isomer or geometrical isomer. These isomers are included in the present invention.

10 The present invention provides a process for producing the compound of the general formula I which comprises (a) reacting a compound of the following structure III:

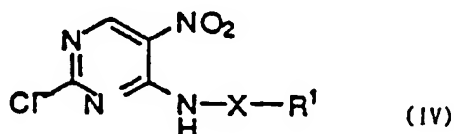


with a compound of the general formula III-a:



20

in which X and R¹ represent the same as defined above, to give a compound of the general formula IV:

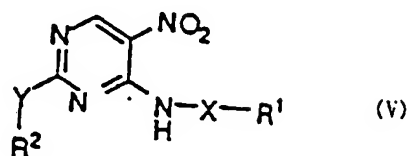


30 in which X and R¹ represent the same as defined above,
(b) reacting the compound IV with a compound of the general formula IV-a:



(IV-a)

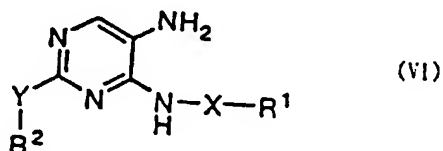
in which Y and R² represent the same as defined above, to give a compound of the general formula V:



10

in which X, R¹ and R² represent the same as defined above,

(c) reducing the compound V to give a compound of the general formula VI:



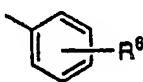
in which X, Y, R¹, and R² represent the same as defined above,

(d-i) reacting the compound VI with a compound of the general formula (VI-1):

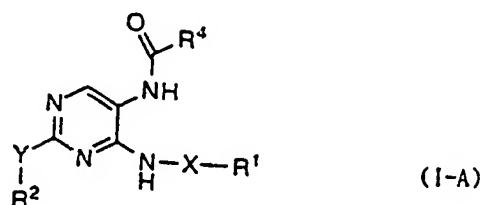
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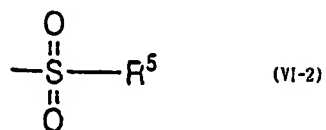
25 in which R⁴ is selected from a group consisting of hydroxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen C₂₋₆ alkenyl and C₁₋₄

alkoxy or R⁴ represents  in which R⁶ is selected from a group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl,

halogen, nitro and C₁₋₄alkoxy to give the compound of the general formula I-A:



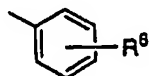
- 10 in which X, Y, R¹, R² and R⁴ are the same as defined above; or
(d-ii) reacting the compound VI with a compound of the general formula (VI-a):



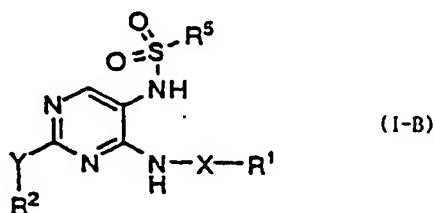
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in which R⁵ is selected from a group consisting of hydroxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen C₂₋₆ alkenyl and C₁₋₄

alkoxy or R⁵ represents



- 20 in which R⁶ is selected from a group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen, nitro and C₁₋₄ alkoxy, to give the compound of the general formula I-B:



in which X, Y, R¹, R² and R⁵ are the same as defined above.

The compound III is described in WO 9510506 and, preferably, can be prepared by reacting the compound II with phosphorus oxychloride in the presence of a base. N,N-diethyl-aniline, N,N-dimethylaniline or N,N-diisopropyl-ethylamine can be used as the base. As such, the reaction is carried out at a reflux temperature.

The compound IV can be prepared by reacting the compound III with the compound of the formula III-a: HN-X-R^1 in which R^1 is the same as defined above, preferably, using pyridine or triethylamine in solvent such as dichloromethane or acetonitrile at 0°C to room temperature (J. Med. Chem. 1994, 37, 2106).

The compound V can be prepared by dissolving the compound IV in a polar solvent and reacting the solution with the compound of the formula IV-a: Y-R^2 in which R^2 is the same as defined above, at 0°C to reflux temperature. Usually, the compound V is obtained as crystals in acetonitrile, ethanol or isopropanol.

The compound VI is obtained by reacting the compound V with iron and acid in polar solvent under reflux (WO 9518097) or by reacting the compound V with sodium borohydride and 5% palladium on activated carbon in solvent such as methanol or ethanol at 0°C to 25°C (Synthesis, 1994, 1437).

The compound I-A is produced by reacting the compound VI with the

compound VI-a: $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—R}^4$ in which R^4 is the same as defined above, using pyridine, triethylamine or N,N-diisopropylethylamine as a base in solvent such as acetonitrile, dichloromethane or tetrahydrofurane at 0°C to reflux

temperature.

The compound I-B is produced by reacting the compound VI with the

compound VI-b: $\begin{array}{c} \text{O} \\ \parallel \\ -\text{S}-\text{R}^5 \\ \parallel \\ \text{O} \end{array}$ in which R^5 is the same as defined above, using pyridine or N,N-diisopropylethylamine as a base in solvent such as acetonitrile, dichloromethane or tetrahydrofuran at 0°C to 25°C.

10 The invention will now be described with reference to the following illustrative Examples.

EXAMPLES

15 **REFERENCE EXAMPLE 1** **2,4-dichloro-5-nitropyrimidine**

25 g of 5-nitrourasil was suspended in 490 ml of phosphorous
oxychloride for 10 minutes and diisopropylethylamine was slowly added to the
20 suspension at room temperature. The reaction suspension was refluxed at 130
°C for 3 hours. The solution was concentrated under reduced pressure to be a
volume of 100 ml. Then, the solution was added dropwise to 500 ml of ice
water and stirred for 1 hour, and extracted with diethyl ether (300 ml × 5).
The organic layer was washed with 500 ml of saturated ammonium chloride
25 and dried over anhydrous magnesium sulfate and concentrated under reduced
pressure. Column chromatography on silica gel (ethyl acetate : hexane=1 : 5)
afforded 16.8 g of the title compound.

NMR (CDCl₃, 400MHz): δ = 8.82(1H,s)

30 **REFERENCE EXAMPLE 2**

4N-benzyl-2-chloro-5-nitropyrimidineamine

2.7ml of benzylamine was added to a solution of 5.0g of the 2,4-dichloro-5-nitropyrimidine (Reference Example 1) in 75ml of dichloromethane at 5°C and the solution was stirred for 1 hour. 3.6ml of triethylamine was added to the solution at 5°C, stirred for 10 minutes, washed with 150 ml of saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain 6.6 g of the title compound.

NMR(CDCl₃, 400MHz): δ = 4.68(2H, d), 7.17(5H, m), 8.65(1H, t), 8.84(1H, s)

REFERENCE EXAMPLE 3**4N-(4-bromobenzyl)-2-chloro-5-nitropyrimidineamine**

2,4-dichloro-5-nitropyrimidine obtained by Reference Example 1 was used as a starting material and was reacted in the same manner as Reference Example 2 to obtain the title compound.

NMR (CDCl₃, 400MHz): δ = 4.81(2H, d), 7.32(2H, d), 7.45(2H, d), 8.61(1H, t), 8.85(1H, s)

REFERENCE EXAMPLE 4**2-chloro-4N-(2-chlorobenzyl)-5-nitropyrimidineamine**

2,4-dichloro-5-nitropyrimidine obtained by Reference Example 1 was used as a starting material and was reacted in the same manner as Reference Example 2 to obtain the title compound.

NMR (CDCl₃, 400MHz): δ = 4.75(2H, d), 7.43(3H, d), 7.48(1H, d), 8.61(1H, t), 8.85(1H, s)

REFERENCE EXAMPLE 5

2-chloro-4N-(1,3-dioxaindan-5-yl)methyl-5-nitropyrimidineamine

3.0 ml of piperonylamine was added to a solution of 5.0 g of 2,4-dichloro-5-nitropyrimidine obtained by Reference Example 1 in 75 ml of dichloromethane at 5°C and the solution was stirred for 1 hour. 3.6 ml of triethylamine was then added to the reaction solution at 5°C, stirred for 10 minutes, washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain 6.9 g of the title compound.

NMR(CDC1₃, 400MHz): δ = 4.60(2H, d), 5.95(2H, s), 6.86(1H, d), 6.91(1H, d), 7.03(1H, d), 8.61(1H, t), 8.85(1H, s).

REFERENCE EXAMPLE 6**Ethyl 1-(4-benzylamino-5-nitropyrimidin-2-yl)-4-piperidinecarboxylate**

3.5 ml of isonipecotate was added to a solution of 1.0 g of 4N-benzyl-2-chloro-5-nitropyrimidineamine (Reference Example 2) in 35 ml of acetonitrile and the suspension was stirred overnight. 35 ml of ethanol was added to the suspension, cooled to 5°C and stirred for 1 hour. Filtration afforded 0.91 g of the yellowish title compound.

NMR(CDC1₃, 400MHz): δ = 1.06(3H, t), 1.51(2H, m), 1.79(2H, ABq), 2.39(1H, m), 2.97(2H, m), 3.95(2H, q), 4.40(2H, d), 4.54(2H, d), 7.15(5H, m), 8.54(1H, t), 8.82(1H, s).

REFERENCE EXAMPLE 7**4N-benzyl-2-(4-ethylpiperazino)-5-nitro-4-pyrimidineamine**

4N-benzyl-2-chloro-5-nitropyrimidineamine (Reference Example 2) was used as a starting material and was reacted in the same manner as Reference Example 6 to obtain the title compound.

NMR(CDC₁₃, 400MHz): δ = 0.93(3H, t), 2.25(6H, m), 3.79(4H, m), 4.55(2H, d), 7.16(5H, m), 8.58(1H, t), 8.81(1H, s)

REFERENCE EXAMPLE 8

5 4N-(4-bromobenzyl)-2-(1H-imidazol-1-yl)-5-nitropyrimidineamine

4N-(4-bromobenzyl)-2-chloro-5-nitropyrimidineamine (Reference Example 3) was used as a starting material and was reacted in the same manner as Reference Example 6 to obtain the title compound.

10 NMR(DMSO-d₆, 400MHz): δ = 4.81(2H, d), 7.07(1H, s), 7.32(2H, d), 7.45(2H, d), 7.79(1H, t), 8.47(1H, s), 9.16(1H, s), 9.67(1H, t)

REFERENCE EXAMPLE 9

15 Ethyl 1-[4-(1,3-dioxaindan-5-yl)methylamino-5-nitropyrimidin-2-yl]-4-piperidinecarboxylate

3.0 ml of ethyl isonipecotatate was added to a solution of 1.0 g of 2-chloro-4N-(1,3-dioxaindan-5-yl)methyl-5-nitropyrimidineamine (Reference Example 5) in 45 ml of acetonitrile at room temperature and the suspension was stirred overnight. 45 ml of ethanol was added to the suspension, cooled to 5°C, and stirred for 1 hour. Filtration afforded 1.0 g of the yellowish title compound.

20 NMR (CDC₁₃, 400MHz): δ = 1.26(3H, t), 1.71(2H, m), 1.97(2H, ABq), 2.58(1H, m), 3.18(2H, m), 4.15(2H, q), 4.52(2H, m), 4.67(2H, d), 5.94(2H, s), 6.7
25 8(3H, m), 8.63(1H, t), 8.98(1H, s)

REFERENCE EXAMPLE 10

30 4N-(1,3-dioxaindan-5-yl)methyl-2-(2-ethyl-4-methyl-1H-imidazol-1-yl)-5-nitropyrimidineamine

The compound prepared by Reference Example 5 was used as a starting material and was reacted in the same manner as Reference Example 9 to obtain the title compound.

NMR (CDCl₃, 400MHz): δ = 1.31(3H, t), 2.24(3H, s), 3.22(2H, q), 4.78(2H, d), 6.00(2H, s); 6.94(3H, m), 7.58(1H, s), 8.72(1H, t), 9.25(1H, s)

REFERENCE EXAMPLE 11

Ethyl 1-[4-(1,3-dioxaindan-5-yl)methylamino-5-nitropyrimidin-2-yl]-4-piperazine carboxylate

2.5 ml of ethyl 1-piperazinecarboxylate was added to a solution of 1.75 g of 2-chloro-4N-(1,3-dioxaindan-5-yl)methyl-5-nitropyrimidineamine (Reference Example 5) in 60 ml of acetonitrile and the suspension was stirred overnight. 100ml of ethanol was added to the suspension, cooled to 5 °C, and stirred for 1.5 hour. Filtration afforded 2.1 g of the title compound.

NMR (CDCl₃, 400MHz): δ = 1.55(3H, t), 3.77(4H, d), 4.01(4H, d), 4.48(2H, q), 4.77(2H, d), 6.10(2H, s), 7.00(2H, d), 7.04(1H, s), 8.25(1H, t), 9.11(1H, s)

REFERENCE EXAMPLE 12

4N-(1,3-dioxaindan-5-yl)methyl-2-(1H-imidazol-1-yl)-5-nitropyrimidineamine

2.3g of 1H-imidazole was added to a solution of 1.75 g of 2-chloro-4N-(1,3-dioxaindan-5-yl)methyl-5-nitropyrimidineamine (Reference Example 5) in 60 ml of acetonitrile and the suspension was stirred overnight. The suspension was concentrated under reduced pressure to obtain solid. The resulting solid was suspended in water : ethanol=40 ml : 100 ml, filtered, and dried to obtain 1.55 g of the title compound.

NMR (CDCl₃, 400MHz): δ = 4.72(2H, d), 6.09(2H, s), 6.98(2H, d), 7.03(1H, s), 7.13(1H, s), 7.80(1H, s), 8.35(1H, t), 8.40(1H, s), 9.18(1H, s)

REFERENCE EXAMPLE 13**4N-benzyl-5-nitro-2-(1H-tetrazol-1-yl)pyrimidineamine**

5 4.0 g of 4N-benzyl-2-chloro-5-nitropyrimidineamine (Reference Example 2) was added to a solution of 3.0g of 1H-tetrazole in 120 ml of acetonitrile. A mixture of 2.5 ml of triethylamine and 45 ml of acetonitrile was added dropwise to the solution. The reaction solution was stirred overnight and was concentrated under reduced pressure to obtain solid. The resulting solid was
10 suspended in 3N sodium hydroxide solution for 1 hour, filtered and dried to obtain 3.80g of the title compound.

NMR (CDCl₃, 400MHz): δ = 4.99(2H, d), 7.44(5H, m), 8.79(1H, t), 9.32(1H, s), 9.48(1H, s)

15 REFERENCE EXAMPLE 14**Ethyl 1-(5-amino-4-benzylaminopyrimidin-2-yl)-4-piperidinecarboxylate**

 1.3 ml of acetic acid, 1.3 ml of distilled water and 1.40 g of iron were added to a suspension of 0.90 g of ethyl 1-[4-benzylamino-5-nitropyrimidin-2-yl)-4-piperidinecarboxylate (Reference Example 6) in 50 ml of
20 ethanol and the reaction solution was refluxed for 5 hours. The dark blue solution was filtered to remove the insoluble substance, and concentrated under reduced pressure to obtain the thin yellow oily product. The resulting product was dissolved in dichloromethane and washed with 10% sodium
25 carbonate(50ml \times 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 0.57 g of the title compound as a oily product.

NMR (DMSO-d₆, 400MHz): δ = 1.04(3H, t), 1.45(2H, m), 1.76(2H, m), 2.41(1H, m), 2.91(2H, m), 3.93(2H, q), 4.40(2H, d), 4.48(2H, d), 5.31(2H, s), 7.20(5H, m), 7.54(1H, t), 7.62(1H, s).
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REFERENCE EXAMPLE 15**4N-benzyl-2-(4-ethylpiperazino)-5-pyrimidinediamine**

5 4N-benzyl-2-(4-ethylpiperazino)-5-nitro-4-pyrimidineamine (Reference Example 7) was used as a starting material and was reacted in the same manner as Reference Example 14 to obtain the title compound.

NMR (CDCl₃, 400MHz): δ = 0.92(3H, t), 2.23(6H, m), 3.75(4H, m), 4.48(2H, d), 5.31(2H, s), 7.15(5H, m), 7.38(1H, t), 7.60(1H, s).

10

REFERENCE EXAMPLE 16**4N-(4-bromobenzyl)-2-(1H-imidazol-1-yl)-5-pyrimidinediamine**

15 The compound prepared by Reference Example 8 was used as a starting material and was reacted in the same manner as Reference Example 14 to obtain the title compound.

NMR (DMSO-d₆, 400MHz): δ = 4.65(2H, D), 5.40(2H, s), 7.07(1H, s), 7.28(2H, d), 7.33(1H, t), 7.43(2H, d), 7.58(1H, s), 7.62(1H, s), 8.47(1H, s).

20

REFERENCE EXAMPLE 17**Ethyl 1-[5-amino-4-(1,3-dioxaindan-5-yl)methylamino]pyrimidin-2-yl]-4-piperidinecarboxylate**

25 5.0 ml of acetic acid, 4.1 ml of distilled water and 4.1 g of iron were added to a suspension of 2.00 g of the compound prepared by Reference Example 9 in 120 ml of ethanol and the suspension was refluxed for 3 hours. The dark blue suspension was filtered to remove the insoluble substance, and concentrated under reduced pressure to obtain the thin yellowish oily product. The resulting product was dissolved in dichloromethane and washed with 10% sodium carbonate(100ml \times 2). The organic layer was dried over anhydrous

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magnesium sulfate, and concentrated under reduced pressure to yield 1.21 g of the thin yellow title compound.

NMR (DMSO-d₆, 400MHz): δ = 1.23(3H, t), 1.69(2H, m), 1.95(2H, q), 2.56(1H, m), 3.17(2H, m), 4.12(2H, q), 4.50(2H, m), 4.67(2H, d), 5.43(2H, s), 5.96(2H, m), 6.76(3H, m), 7.58(1H, t), 7.65(1H, s).

REFERENCE EXAMPLE 18

4N-(1,3-dioxaindan-5-yl)methyl-2-(2-ethyl-4-methyl-1H-imidazol-1-yl)-5-pyrimidinediamine

The compound prepared by Reference Example 10 was used as a starting material and was reacted in the same manner as Reference Example 14 to obtain the title compound.

NMR (DMSO-d₆, 400MHz): δ = 1.20(3H, t), 2.27(3H, s), 3.17(2H, q), 4.55(2H, d), 5.33(2H, s), 5.98(2H, s), 6.86(2H, q), 6.93(1H, s), 7.60(1H, s), 7.77(1H, s), 7.93(1H, t).

REFERENCE EXAMPLE 19

Ethyl 1-[5-amino-4-(1,3-dioxaindan-5-yl)methylaminopyrimidin-2-yl]-4-piperazinecarboxylate

10.0 ml of acetic acid, 5.0 ml of distilled water and 4.01 g of iron were added to a suspension of 3.00 g of the compound prepared by Reference Example 11 in 150 ml of ethanol and the suspension was refluxed for 3 hours. The dark blue suspension was filtered to remove the insoluble substance, and concentrated under reduced pressure to obtain the thin yellow oily product. The resulting product was dissolved in dichloromethane and washed with 10% sodium carbonate(150ml \times 2). The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Column chromatography on silica gel (methanol : dichloromethane = 1 : 10)

afforded 2.0 g of the title compound as a thin yellow solid.

NMR (DMSO-d₆, 400MHz): δ = 1.52(3H, t), 3.75(4H, d), 4.00(4H, d), 4.46(2H, q), 4.70(2H, d), 5.38(2H, s), 6.08(2H, s), 6.97(2H, d), 7.02(1H, s), 7.45(1H, t), 7.65(1H, s)

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REFERENCE EXAMPLE 20

4N-(1,3-dioxaindan-5-yl)methyl-2-(1H-imidazol-1-yl)-5-pyrimidinediamine

The compound prepared by Reference Example 12 was used as a starting material and was reacted in the same manner as Reference Example 14 to obtain the title compound.

NMR (DMSO-d₆, 400MHz): δ = 4.68(2H, d), 5.38(2H, s), 6.05(2H, s), 6.97(2H, d), 7.02(1H, s), 7.13(1H, s), 7.46(1H, t), 7.67(1H, s), 7.80(1H, s), 8.37(1H, s)

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REFERENCE EXAMPLE 21

4N-benzyl-2-(1H-tetrazol-1-yl)-5-pyrimidinediamine

The compound prepared by Reference Example 13 was used as a starting material and was reacted in the same manner as Reference Example 14 to obtain the title compound.

NMR (DMSO-d₆, 400MHz): δ = 4.72(2H, d), 5.36(2H, s), 7.28(1H, t), 7.34(2H, t), 7.43(2H, t), 7.63(1H, s), 7.65(1H, t), 9.94(1H, s)

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EXAMPLE 1

1-[4-benzylamino-5-(2-bromophenylsulfonamido)pyrimidin-2-yl]-4-piperidine-carboxylic acid

230 mg of 2-bromobenzenesulfonyl chloride was added to a solution of 400 mg of the compound prepared by the Reference Example 14 in 40 ml of

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ethanol at room temperature and the solution was stirred for 10 minutes. 0.27 ml of pyridine was added to the yellow reaction solution, stirred at room temperature overnight, and concentrated under reduced pressure to remove the solvent. The oily product obtained therefrom was mixed with 50 ml of dichloromethane and washed with saturated sodium carbonate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (ethyl acetate : hexane=1 : 1) afforded 170 mg of the pink solid ester compound.

150 mg of the ester compound was dissolved in 30 ml of methanol. 15 ml of 1.5N sodium hydroxide was added to the solution and stirred for 30 minutes at room temperature. The reaction solution was concentrated under reduced pressure to remove the organic solvent. Then, the aqueous layer was adjusted to pH4.0 by using 3.0 N hydrochloric acid and stirred for 30 minutes. Filtration afforded 110 mg of the title compound as a white solid. m.p. 114-117°C.

NMR (DMSO-d₆, 400MHz): δ = 1.28(2H, m), 1.71(2H, m), 2.40(1H, m), 2.81(2H, t), 4.30(2H, d), 4.46(2H, d), 7.01(1H, s), 7.21(1H, m), 7.27(5H, m), 7.52(2H, m), 7.89(2H, m), 9.40(1H, s), 12.35(1H, s).

EXAMPLE 2

1-[4-benzylamino-5-(4-bromophenylsulfonamido)pyrimidin-2-yl]-4-piperidine-carboxylic acid

210 mg of 4-bromobenzenesulfonyl chloride was added to a solution of 300 mg of the compound prepared by the Reference Example 14 in 40 ml of dichloromethane at room temperature and the solution was stirred for 10 minutes. 0.20 ml of pyridine was added to the yellow reaction solution, stirred for 30 hours at room temperature, washed with 50 ml of saturated sodium carbonate, and the organic layer was dried over anhydrous magnesium

sulfate and concentrated under reduced pressure. The oily resulting material was purified by column chromatography on silica gel (methanol : dichloromethane=7.5% v/v) to obtain 300 mg of the yellow solid ester compound.

5

250 mg of the ester compound was dissolved in 30 mg of ethanol. 15 ml of 1.5N sodium hydroxide was added to the solution and stirred for 3.5 hours at room temperature. The reaction solution was concentrated under reduced pressure to remove the organic solvent. Then, the aqueous layer was adjusted to pH 4.0 by using 3.0 N hydrochloric acid and stirred for 1 hour at 5°C. Filtration afforded 110 mg of the title compound as a white solid. m.p. 136-138°C.

10 NMR (DMSO-d₆, 400MHz): δ = 1.36(2H, m), 1.76(2H, m), 2.45(1H, m), 2.91(2H, t), 4.25(2H, d), 4.40(2H, d), 7.11(1H, s), 7.23(5H, m), 7.53(1H, s), 7.70
15 (2H, d), 7.80(2H, d), 9.58(1H, s), 12.48(1H, brs).

EXAMPLE 3

1-[4-benzylamino-5-(4-methylphenylsulfoneamido)pyrimidin-2-yl]-4-piperidine-carboxylic acid

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180 mg of p-toluenesulfonyl chloride was added to a solution of 280 mg of the compound prepared by the Reference Example 14 in 40 ml of dichloromethane at room temperature and the solution was stirred for 10 minutes. 0.20 ml of pyridine was added to the yellow reaction solution, and stirred for 14 hours at room temperature. The solution was washed with 30 ml of 1.5 N sodium hydroxide, the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 450 mg of the yellow solid ester compound.

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450 mg of the ester compound was dissolved in 50 mg of ethanol. 25

ml of 1.5 N sodium hydroxide was added to the solution and stirred for 2.5 hours at room temperature to complete the hydrolysis reaction. The reaction solution was concentrated under reduced pressure to remove the organic solvent. The aqueous layer was adjusted to pH 3.5 by using 3.0 N hydrochloric acid and stirred for 1 hour at 5°C. Filtration afforded 170 mg of the title compound as a white solid. m.p. 126-127°C

NMR (DMSO-d₆, 400MHz): δ = 1.31(2H, m), 1.72(2H, m), 2.39(3H, s), 2.41(1H, m), 2.82(2H, t), 4.31(2H, d), 4.40(2H, d), 7.02(1H, s), 7.10(1H, t), 7.28(5H, m), 7.38(2H, d), 7.63(2H, d), 9.04(1H, s), 12.20(1H, s)

EXAMPLE 4

1-[4-benzylamino-5-(4-chlorophenylcarboxamido)pyrimidin-2-yl]-4-piperidine-carboxylic acid

The compound prepared by Reference Example 14 and 4-chlorobenzoyl chloride were used as starting materials and were reacted in the same manner as in Example 3 to obtain the title compound. m.p. 155-157°C

NMR (DMSO-d₆, 400MHz): δ = 1.48(2H, m), 1.85(2H, m), 2.56(1H, m), 3.14(2H, t), 4.29(2H, d), 4.58(2H, d), 7.23(1H, t), 7.35(5H, m), 7.50(2H, d), 7.80(1H, s), 8.06(2H, d), 9.99(1H, s), 12.39(1H, s).

EXAMPLE 5

1-(4-benzylamino-5-hexylcarboxamidopyrimidin-2-yl)-4-piperidinecarboxylic acid

The compound prepared by Reference Example 14 and hexanoyl chloride were used as starting materials and were reacted in the same manner as Example 3 to obtain the title compound. m.p. 245°C (decomposition)

NMR (DMSO-d₆, 400MHz): δ = 0.86(3H, t), 1.27(3H, m), 1.34(3H, m), 1.57(2H, t), 1.64(2H, d), 2.00(1H, m), 2.27(2H, t), 2.85(2H, t), 4.31(2H, d),

4.48(2H, d), 7.18(1H, t), 7.33(5H, m), 7.62(1H, s), 9.24(1H, s), 12.42(1H, s).

EXAMPLE 6

1-(4-benzylamino-5-ethylsulfonamidopyrimidin-2-yl)-4-piperidinecarboxylic acid

5

The title compound was obtained according to the procedure of Example 3 by using the compound prepared by Reference Example 14 and ethanesulfonyl chloride as starting materials. m.p. 205°C

10 NMR(DMSO-d₆, 400MHz): δ = 1.22(3H, t), 1.33(2H, m), 1.75(2H, m), 2.45(1H, m), 2.88(2H, t), 3.04(2H, q), 4.40(2H, d), 4.49(2H, d), 7.21(1H, t), 7.30(5H, m), 7.66(1H, s), 8.54(1H, s), 12.22(1H, s).

EXAMPLE 7

15 1-(4-benzylamino-5-trifluoromethylsulfonamidopyrimidin-2-yl)-4-piperidine-carboxylic acid

350 mg of the compound prepared by Reference Example 14 was dissolved in 40 ml of dichloromethane and the solution was cooled to -70°C under nitrogen atmosphere. 0.27 ml of triethylamine and 0.20 ml of trifluoromethanesulfonic anhydride were added to the solution and stirred for 1.5 hour at -70°C. The reaction solution was warmed to room temperature and washed with 30 ml of 1.5 N sodium hydroxide. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain the oily product. Column chromatography over silica gel (methanol : dichloromethane=7.5% v/v) afforded 280 mg of ester compound.

250 mg of the ester compound was dissolved in 30 ml of ethanol. 15 ml of 1.5 N sodium hydroxide was added to the solution, and stirred under reflux for 3.5 hours. The reaction solution was concentrated under reduced

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pressure to remove the organic solvent. The aqueous layer was adjusted to pH 3.5 by using 3.0 N hydrochloric acid and was stirred for 1 hour at 5°C. Filtration afforded 160 mg of the title compound as a white solid. m.p. 160°C
NMR (DMSO-d₆, 400MHz): δ = 1.37(2H, m), 1.78(2H, m), 2.43(1H, m),
5 2.90(2H, t), 4.42(2H, d), 4.48(2H, d), 7.24(1H, t), 7.38(5H, m), 7.70(1H, s), 9.21(1H, s), 12.40(1H, brs).

EXAMPLE 8

10 **4-benzylamino-5-(2-bromophenylsulfonamido)-2-(4-ethylpiperazino)pyrimidine hydrochloride**

120 mg of the pre-base of the title compound was prepared by using the compound obtained by the Reference Example 15 and 2-bromobenzenesulfonyl chloride as starting materials according to the
15 procedure of Example 3 and was dissolved in 15 ml of methanol. 4 ml of 5% HCl-methanol was added to the solution and stirred for 30 minutes at room temperature. The reaction solution was concentrated under reduced pressure to remove the solvent. Crystallization with diethyl ether and petroleum ether afforded 95 mg of the title trihydrochloride compound. m.p. 67-70°C
20 NMR (DMSO-d₆, 400MHz): δ = 1.18(3H, t), 2.50(6H, m), 3.79(4H, m), 4.69(2H, d), 6.12(1H, t), 7.30(5H, m), 7.40(1H, s), 7.49(2H, q), 7.82(1H, q), 8.80(1H, q).

EXAMPLE 9

25 **4-benzylamino-5-(4-chlorophenylsulfonamido)-2-(4-ethylpiperazino)-pyrimidine hydrochloride**

230 mg of the pre-base of the title compound was obtained by using the compound prepared by the Reference Example 15 and
30 4-chlorobenzenesulfonyl chloride as starting materials according to the

procedure of Example 3 and was dissolved in 25 ml of methanol. 7 ml of 5% HCl-methanol was added to the solution and stirred for 30 minutes at room temperature. The reaction solution was concentrated under reduced pressure to remove the solvent. Crystallization with diethyl ether and petroleum ether afforded 180 mg of the title trihydrochloride compound. m.p. 78-81°C
5 NMR (DMSO-d₆, 400MHz): δ = 0.98(3H, t), 2.28(6H, m), 3.38(4H, m), 4.43(2H, d), 6.59(1H, t), 7.23(5H, m), 7.33(2H, q), 7.36(1H, s), 7.61(2H, q).

EXAMPLE 10

10 **5-(4-chlorophenylsulfonamido)-4-(4-bromobenzylamino)-2-(1H-imidazol-1-yl) pyrimidine**

15 150 mg of 4-chlorobenzenesulfonyl chloride was added to a solution of 220 mg of the compound prepared by the Reference Example 16 in 40 ml of dichloromethane at room temperature and stirred for 10 minutes. 0.13 ml of pyridine was added to the reaction solution, stirred for 30 minutes at room temperature and washed with 40 ml of 1.5 N sodium hydroxide. The organic layer was washed with 1N hydrochloric acid to remove the impure substance. The organic layer was dried over anhydrous magnesium sulfate and
20 concentrated under reduced pressure to obtain thin yellow oily product. Crystallization with diethyl ether and petroleum ether afforded 186 mg of the title compound. m.p. 183-185°C
NMR (DMSO-d₆, 400MHz): δ = 4.72(2H, d), 7.40(2H, d), 7.53(2H, d), 7.59(1H, s), 7.66(2H, d), 7.76(2H, d), 7.78(1H, t), 8.13(1H, t), 8.19(1H, d), 8.24(1H, d),
25 9.24(1H, s).

EXAMPLE 11

Ethyl 1-[5-(2-bromophenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylamino-pyrimidin-2-yl]-4-piperidinecarboxylate

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180 mg of 2-bromobenzenesulfonyl chloride was added to a solution of 310 mg of the compound prepared by the Reference Example 17 in 50 ml of ethanol at room temperature and stirred for 10 minutes. The yellowish reaction solution was further stirred for 55 hours at room temperature and concentrated under reduced pressure to remove the solvent. The oily product obtained therefrom was mixed with 70 ml of chloroform and washed with saturated sodium carbonate(100 ml×2). The organic layer was dried over anhydrous magnesium sulfate and was concentrated under reduced pressure to obtain oily product. Column chromatography on silica gel (ethyl acetate : hexane=1 : 1) afforded 290 mg of the title compound as a solid. m.p. 160-161℃
NMR(CDC1₃, 400MHz): δ =1.17(3H, t), 1.57(2H, m), 1.80(2H, ABq), 2.41(1H, m), 2.85(2H, m), 4.05(2H, q), 4.40(2H, t), 4.44(2H, d), 5.88(2H, s), 5.90(1H, t), 6.71(3H, m), 7.15(1H, s), 7.35(2H, m), 7.68(1H, m), 7.83(1H, m).

EXAMPLE 12

1-[5-(4-chloropenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidin-2-yl]-4-piperidinecarboxylic acid

140 mg of 4-chlorobenzenesulfonyl chloride was added to a solution of 260 mg of the compound prepared by the Reference Example 17 in 40 ml of dichloromethane at room temperature and stirred for 10 minutes. 0.15 ml of pyridine was added to the reaction solution, and stirred for 45 hours at room temperature and washed with 30 ml of 1.5 N sodium hydroxide. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 250 mg of the ester compound as a yellow solid.

250 mg of the ester compound was dissolved in 30 ml of ethanol. 15 ml of 1.5 N sodium hydroxide was added to the solution and stirred for 30 minutes at room temperature. The reaction solution was concentrated under reduced pressure to remove the organic layer. The aqueous layer was adjusted

to pH 4.5 by using 3.0 N hydrochloric acid and stirred for 1 hour at 5°C. Filtration afforded 85 mg of the title compound as a white solid. m.p. 209-210°C.

5 NMR(DMSO-d₆, 400MHz): δ = 1.49(2H, m), 1.89(2H, m), 2.69(1H, m), 3.14(2H, m), 4.19(2H, brs), 4.41(2H, d), 6.00(2H, s), 6.72(1H, d), 6.83(1H, d), 6.85(1H, d), 6.97(1H, s), 7.67(2H, m), 7.83(2H, m), 8.90(1H, brs), 9.96(1H, brs).

EXAMPLE 13

10 **5-(2-chloropenylcarboxamido)-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-2-ethyl -4-methylimidazol-1-yl)pyrimidine**

The title compound was obtained according to the procedure of Example 10 by using the compound prepared by Reference Example 18 and 2-chlorobenzoyl chloride as starting materials. m.p.: 152-154°C

15 NMR (DMSO-d₆, 400MHz): δ = 1.24(3H, t), 2.30(3H, d), 3.27(2H, q), 4.60(2H, d), 5.97(2H, s), 6.87(2H, d), 6.99(1H, s), 7.54(3H, M), 7.82(1H, q), 7.92(1H, d), 8.33(1H, t), 8.50(1H, s), 10.29(1H, s).

20 EXAMPLE 14

5-(2,4-dinitrophenylcarboxamido)-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-2-ethyl-4-methylimidazol-1-yl)pyrimidine

25 The title compound was obtained according to the procedure of Example 10 by using the compound prepared by Reference Example 18 and 2,4-dinitrobenzoyl chloride as starting materials. m.p.: 170-171°C

30 NMR (DMSO-d₆, 400MHz): δ = 1.27(3H, t), 2.32(3H, d), 3.34(2H, q), 4.60(2H, d), 5.98(2H, s), 6.90(2H, d), 6.98(1H, s), 8.32(1H, s), 8.45(1H, t), 8.52(1H, s), 9.22(2H, d), 10.27(1H, s), 10.66(1H, s).

EXAMPLE 15

Ethyl 1-[5-(4-bromophenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylamino-pyrimidin-2-yl]-4-piperazinecarboxylate

- 5 180 mg of 4-bromobenzenesulfonyl chloride was added to a solution of
250 mg of the compound prepared by the Reference Example 19 in 40 ml of
dichloromethane at room temperature and stirred for 10 minutes. 0.15 ml of
pyridine was added to the yellow reaction solution, and stirred for 30 hours at
room temperature and washed with 50 ml of 1.5 N sodium hydroxide. The
10 organic layer was dried over anhydrous magnesium sulfate and concentrated
under reduced pressure to obtain oily product. The residue was purified by
column chromatography on silica gel (methanol : dichloromethane=7.5% v/v).
Crystallization with diethyl ether and petroleum ether afforded 165 mg of the
title compound. m.p. 173-176°C
- 15 NMR (CDCl₃, 400MHz): δ = 1.52(3H, t), 3.73(4H, d), 3.96(4H, d), 4.40(2H, q),
4.75(2H, d), 6.18(1H, t), 6.21(2H, s), 7.02(2H, d), 7.06(1H, s), 7.51(1H, s), 7.
89(4H, m), 8.05(1H, t), 8.45(1H, t), 9.11(1H, s).

EXAMPLE 16

- 20 **5-(4-chloropenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-
amidazol-1-yl)pyrimidine**

- 140 mg of 4-chlorobenzenesulfonyl chloride was added to a solution of
210 mg of the compound prepared by the Reference Example 20 in 60 ml of
25 dichloromethane at room temperature and stirred for 10 minutes. 0.15 ml of
pyridine was added to the reaction solution, and stirred for 24 hours at room
temperature and washed with 40 ml of 1.5 N sodium hydroxide. The organic
layer was washed with 1N hydrochloric acid to remove the impure material.
The organic layer was dried over anhydrous magnesium sulfate and
30 concentrated under reduced pressure to obtain thin yellow oily product.

Crystallization with diethyl ether and petroleum ether afforded 130 mg of the title compound. m.p. 206-207°C

NMR (DMSO-d₆, 400MHz): δ = 4.45(2H, d), 5.97(2H, s), 6.76(1H, d), 6.83(1H, d), 6.89(1H, t), 7.05(1H, s), 7.47(1H, s), 7.65(2H, d), 7.74(2H, d), 7.76(1H, s), 7.97(1H, t), 8.40(1H, s), 9.69(1H, s).

EXAMPLE 17

5-ethylsulfoneamido-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-imidazol-1-yl)-pyrimidine

10

The title compound was obtained according to the procedure of Example 16 by using the compound prepared by Reference Example 20 and ethane-sulfonyl chloride as starting materials. m.p.: 188-190°C

NMR(DMSO-d₆, 400MHz): δ = 1.24(3H, t), 3.18(2H, q), 4.57(2H, d), 5.97(2H, s), 6.86(1H, d), 6.94(1H, d), 7.02(1H, d), 7.08(1H, q), 7.82(1H, t), 8.03(1H, s), 8.05(1H, t), 8.45(1H, t), 9.11(1H, brs).

EXAMPLE 18

5-hexylcarboxamido-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-imidazol-1-yl)-pyrimidine

20

The title compound was obtained according to the procedure of Example 16 by using the compound prepared by Reference Example 20 and hexanoyl chloride as starting materials. m.p. 148-150°C

NMR(DMSO-d₆, 400MHz): δ = 0.90(3H, t), 1.14(4H, m), 1.60(2H, m), 2.35(2H, t), 4.56(2H, d), 5.96(2H, s), 6.86(1H, d), 6.91(1H, d), 7.03(1H, d), 7.07(1H, s), 7.81(1H, s), 7.83(1H, t), 8.09(1H, d), 8.32(1H, s), 9.22(1H, s).

EXAMPLE 19

4-benzylamino-5-(4-bromophenylsulfonamido)-2-(1H-tetrazol-1-yl)pyrimidine

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310 mg of 4-bromobenzenesulfonyl chloride was added to a solution of 270 mg of the compound prepared by the Reference Example 21 in 100 ml of acetonitrile at room temperature, and stirred for 10 minutes. 0.24 ml of pyridine was added to the solution, stirred for 40 hours at room temperature and concentrated under reduced pressure to remove acetonitrile. The residue was suspended in 30 ml of methanol, washed with 40 ml of 1.5 N sodium hydroxide, and filtered to obtain 186 mg of the title compound as a white solid. m.p. 184°C

NMR (DMSO-d₆, 400MHz): δ = 4.58(2H, d), 7.31(5H, m), 7.71(2H, d), 7.76(1H, s), 7.78(2H, d), 8.38(1H, t), 9.97(1H, s), 10.06(1H, s).

EXAMPLE 20

4-benzylamino-5-(2,4-dinitrophenylcarboxamido)-2-(1H-tetrazol-1-yl)-pyrimidine

310 mg of dinitrobenzoyl chloride was added to a solution of 270 mg of the compound prepared by the Reference Example 21 in 100 ml of acetonitrile at room temperature and stirred for 10 minutes. 0.24 ml of pyridine was added to the solution, stirred for 40 hours at room temperature, and concentrated under reduced pressure to remove acetonitrile. The residue was suspended in 30 ml of methanol, washed with 40 ml of 1.5 N sodium hydroxide, and extracted with 50 ml of dichloromethane. The organic layer was washed with 50 ml of 1N hydrochloric acid to remove the impure material. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 186 mg of the title compound as a white solid. m.p. 235°C (decomposition)

NMR (DMSO-d₆, 400MHz): δ = 4.77(2H, d), 7.23(1H, t), 7.33(2H, t), 7.45(2H, d), 8.32(1H, s), 8.58(1H, t), 9.05(1H, s), 9.20(2H, d), 10.11(1H, s), 10.69(1H, s).

EXAMPLE 21**4-benzylamino-5-(hexylcarboxamido)-2-(1H-tetrazol-1-yl)pyrimidine**

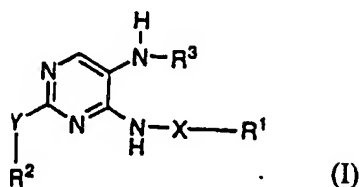
5 310 mg of hexanoyl chloride was added to a solution of 270 mg of
the compound prepared by the Reference Example 21 in 100 ml of acetonitrile
at room temperature and stirred for 10 minutes. 0.24 ml of pyridine was
added to the solution, stirred for 40 hours at room temperature, and
concentrated under reduced pressure to remove acetonitrile. The residue was
10 suspended in 30 ml of methanol, washed with 40 ml of 1.5 N sodium
hydroxide, and extracted with 50 ml of dichlormethane. The organic layer was
washed with 50 ml of 1N hydrochloric acid to remove the impure material.
The organic layer was dried over anhydrous magnesium sulfate and
concentrated under reduced pressure to obtain 186 mg of the title compound
15 as a white solid. m.p. 144-145 °C
NMR (DMSO-d₆, 400MHz): δ = 0.89(3H, t), 1.31(4H, m), 1.59(2H, t), 2.38(2
H, t), 4.46(2H, d), 7.25(1H, t), 7.33(2H, t), 7.45(2H, d), 8.10(1H, d), 8.34(1H,
s), 9.35(1H, s), 10.06(1H, s).

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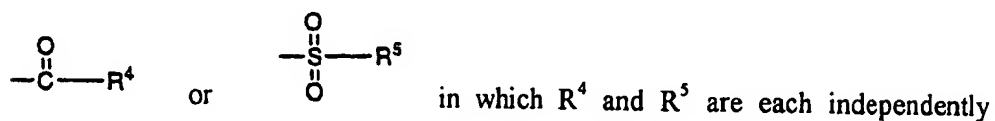
25

WHAT IS CLAIMED IS:

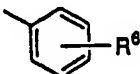
1. A compound of the general formula I:



- 10 or physiologically acceptable salt thereof in which X is a direct bond, C₁₋₄ alkylene, C₁₋₄ alkyleneoxy, C₁₋₄ alkoxyphenyl or phenyl C₁₋₄ alkylene; Y is a direct bond or C₁₋₂ alkyl; R¹ is (i) 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two
 15 selected from a group consisting of hydrogen, halogen, nitro, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy, (ii) C₄₋₁₀ carbocyclic compound or (iii) hydroxy C₁₋₄ alkoxy; R² is 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two
 20 selected from a group consisting of hydrogen, hydroxy, halogen, nitro, hydroxy C₁₋₅ alkyl, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy; R³ is hydrogen,



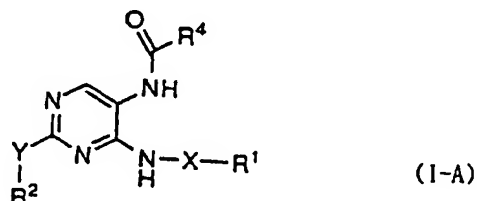
- 25 selected from a group consisting of hydroxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen C₂₋₆ alkenyl and C₁₋₄ alkoxy or R⁴ and R⁵

represent each independently  in which R⁶ is selected from a
 30 group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, halogen C₁₋₆

alkyl, halogen, nitro and C₁₋₄alkoxy.

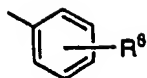
2. The compound of claim 1 which is selected from a group consisting of
- 1-[4-benzylamino-5-(2-bromophenylsulfonamido)pyrimidin-2-yl]-4-piperidine-
5 carboxylic acid;
- 1-[4-benzylamino-5-(4-bromophenylsulfonamido)pyrimidin-2-yl]-4-piperidine-
carboxylic acid;
- 1-[4-benzylamino-5-(4-methylphenylsulfonamido)pyrimidin-2-yl]-4-piperidine-
carboxylic acid;
- 10 1-[4-benzylamino-5-(2-chlorophenylsulfonamido)pyrimidin-2-yl]-4-piperidine-
carboxylic acid;
- 1-(4-benzylamino-5-hexylcarboxamidopyrimidin-2-yl)-4-piperidinecarboxylic acid;
- 1-(4-benzylamino-5-ethylsulfonamidopyrimidin-2-yl)-4-piperidinecarboxylic acid;
- 1-[4-benzylamino-5-trifluoromethylsulfonamidopyrimidin-2-yl]-4-piperidine-
15 carboxylic acid;
- ethyl 1-[5-(2-bromophenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylamino-
pyrimidin-2-yl]-4-piperidinecarboxylate;
- 1-[5-(4-chlorophenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidin
-2-yl]-4-piperidinecarboxylic acid;
- 20 5-(4-chlorophenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-
imidazol-1-yl)pyrimidine;
- 5-ethylsulfonamido-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-imidazol-1-yl)-
pyrimidine;
- 5-hexylcarboxamido-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-imidazol-1-yl)-
25 pyrimidine;
- ethyl 1-[5-(4-bromophenylsulfonamido)-4-(1,3-dioxaindan-5-yl)methylamino-
pyrimidin-2-yl]-4-piperazinecarboxylate;
- 5-(4-chlorophenylsulfonamido)-4N-(4-bromobenzylamino)-2-(1H-imidazol-1-yl)-
pyrimidine;
- 30 5-(2-chlorophenylcarboxamido)-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-2-ethyl

- 4-methylimidazol-1-yl)pyrimidine;
 5-(2,4-dinitrophenylcarboxamido)-4-(1,3-dioxaindan-5-yl)methylamino-2-(1H-2-ethyl-4-methylimidazol-1-yl)pyrimidine;
 4-benzylamino-5-(2-bromophenylsulfonamido)-2-(1H-tetrazol-1-yl)pyrimidine;
 5 4-benzylamino-5-(2,4-dinitrophenylcarboxamido)-2-(1H-tetrazol-1-yl)pyrimidine;
 4-benzylamino-5-(2-hexylcarboxamido)-2-(1H-tetrazol-1-yl)pyrimidine;
 4-benzylamino-5-(2-bromophenylsulfonamido)-2-(4-ethylpiperazino)pyrimidine; or
 4-benzylamino-5-(4-chlorophenylsulfonamido)-2-(4-ethylpiperazino)pyrimidine;
- 10 3. A process for producing a compound of the general formula I-A:



- in which X is a direct bond, C₁₋₄ alkylene, C₁₋₄ alkyleneoxy, C₁₋₄ alkoxyphenyl or phenyl C₁₋₄ alkylene; Y is a direct bond or C₁₋₂ alkyl; R¹ is (i) 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, halogen, nitro, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy, (ii) C₄₋₁₀ carbocyclic compound or (iii) hydroxy C₁₋₄ alkoxy; R² is 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, hydroxy, halogen, nitro, hydroxy C₁₋₅ alkyl, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy; R⁴ is selected from a group consisting of hydroxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen C₂₋₆ alkenyl

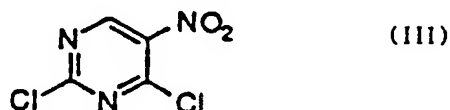
and C₁₋₄ alkoxy or R⁴ represents



in which R⁶ is selected from

a group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen, nitro and C₁₋₄alkoxy, which comprises

5 (a) reacting a compound of the following structure III:

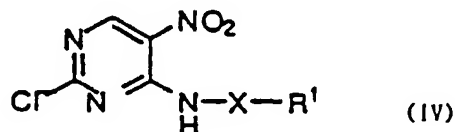


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with a compound of the general formula III-a:



15 in which X and R¹ represent the same as defined above, to give a compound of the general formula IV:



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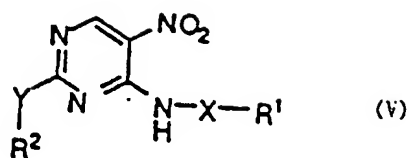
in which X and R¹ represent the same as defined above,

(b) reacting the compound IV with a compound of the general formula IV-a:



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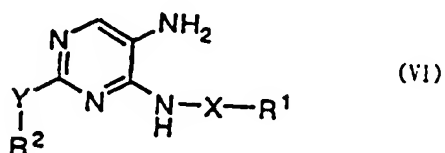
in which Y and R² represent the same as defined above, to give a compound of the general formula V:



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in which X, R¹ and R² represent the same as defined above,

(c) reducing the compound V to give a compound of the general formula VI:



in which X, Y, R¹, and R² represent the same as defined above,

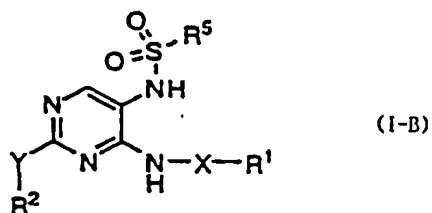
(d) reacting the compound VI with a compound of the general formula (VI-1):



in which R⁴ represents the same as defined above, to give the above compound I.

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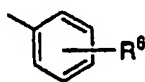
4. A process for producing a compound of the general formula I-B:



in which X is a direct bond, C₁₋₄ alkylene, C₁₋₄ alkyleneoxy, C₁₋₄ alkoxyphenyl

or phenyl C₁₋₄ alkylene; Y is a direct bond or C₁₋₂ alkyl; R¹ is (i) 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, halogen, nitro, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy, (ii) C₄₋₁₀ carbocyclic compound or (iii) hydroxy C₁₋₄ alkoxy; R² is 5-15 membered cyclic or branched chain heterocompound which includes one or two selected from a group consisting of nitrogen, oxygen and sulfur and which is substituted with one or two selected from a group consisting of hydrogen, hydroxy, halogen, nitro, hydroxy C₁₋₅ alkyl, C₁₋₆ alkyl, C₃₋₆ alkenyl and halogen C₁₋₄ alkoxy; R⁵ is selected from a group consisting of hydroxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen C₂₋₆ alkenyl

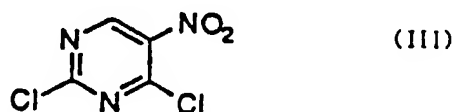
and C₁₋₄ alkoxy or R⁵ represents



in which R⁶ is selected from

a group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, halogen C₁₋₆ alkyl, halogen, nitro and C₁₋₄alkoxy, which comprises

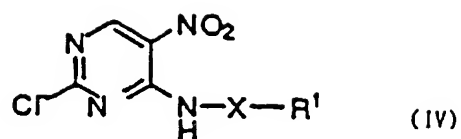
(a) reacting a compound of the following structure III:



with a compound of the general formula III-a:



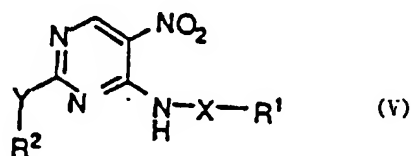
in which X and R¹ represent the same as defined above, to give a compound of the general formula IV:



- 5 in which X and R¹ represent the same as defined above,
 (b) reacting the compound IV with a compound of the general formula IV-a:

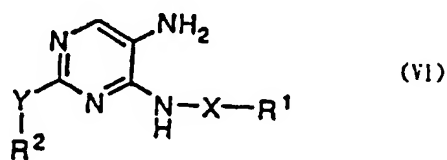


- 10 in which Y and R² represent the same as defined above, to give a compound of the general formula V:

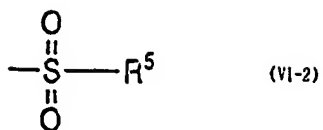


in which X, Y, R¹ and R² represent the same as defined above,

- (c) reducing the compound V to give a compound of the general formula VI:
- 20



- 25 in which X, Y, R¹, and R² represent the same as defined above,
 (d) reacting the compound VI with a compound of the general formula (VI-a):



5 in which R⁵ represents the same as defined above, to give the above compound I.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 97/00155

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: C 07 D 239/48, 403/04, 403/06, 239/50, 401/04, 401/06, 405/04, 409/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: C 07 D 239/00, 401/00, 405/00, 409/00, 403/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 640 599 A1 (ONO PHARMACEUTICAL CO., LTD.) 01 March 1995 (01.03.95), claims 1-9; page 14, line 50 (cited in the application).	1-4
A	EP 0 206 415 A2 (JANSSEN PHARMACEUTICA N.V.) 30 December 1986 (30.12.86), claims; formulas III and VIa; example 3.	1-4
A	US 3 457 263 A (GILBERT) 22 July 1969 (22.07.69), formula V; examples 23, 24.	1-4
A	GB 1 021 195 A (CIBA) 02 March 1966 (02.03.66), examples 1, 7.	1, 2
A	Chemical Abstracts, Vol. 119, No. 15, 11 October 1993 (Columbus, Ohio, USA), page 34, column 1, abstract No. 151742v, LEE, M. et al.: "DNA sequence selective alkylation and cytotoxicity of monoheterocyclic analogs of Hoechst 33258", & Med. Chem. Res. 1993, 3(2), 79-86. (RN 124732-31-6)	1, 2
A	Chemical Abstracts, Vol. 56, No. 1, 08 January 1962 (Columbus, Ohio, USA), column 470, abstract No. 470c,	1, 2

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 November 1997 (04.11.97)

Date of mailing of the international search report

10 November 1997 (10.11.97)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 97/00155

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RN 93871-79-5, H. GOLDNER et al.: "Synthesis of 9-substituted purine derivatives. I. 2,9-, 2,6,9-, and 6,9-substituted purines", & Chem. 12, 242-52(1961). Chemical Abstracts, Vol.54, No.12, 25 June 1960 (Columbus, Ohio, USA), column 12262, abstract No.12262i, RN 93871-79-5, RALPH E. KUNKEE: "Stimulation of enzyme induction by 5-amino-2,4-bis(substituted-amino)=pyrimidines", & J.Bacteriol. 79, 43-50(1960).	1,2
A	Chemical Abstracts, Vol.77, No.21, 20 November 1972 (Columbus, Ohio, USA), page 442, column 2, abstract No.139981d, REGNIER, G. et al.: "Central nervous system depressants. New purine derivatives", & Chim. Ther. 1972, 7(3), 192-205 (Fr). (RN 37419-51-5) ----	1,2

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR 97/00155

1a Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche		Datum der Veröffentlichung Publication date Date de publication		Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets		Datum der Veröffentlichung Publication date Date de publication	
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				CN	A	1109055	27-06-95
				JP	A2	7089958	04-04-95
				US	A	5525604	11-06-96
EP A2	206415	30-12-86		AT	E	85055	15-02-93
				AU	A1	59191786	08-01-87
				AU	E2	588890	28-09-89
				CA	A1	1267889	17-04-90
				DE	CO	3687601	11-03-93
				DE	T2	3687601	03-06-93
				DK	A0	2952786	23-06-86
				DK	A	2952786	25-12-86
				DK	B1	1690734	08-08-94
				EP	A3	206415	16-03-88
				EP	B1	206415	27-01-87
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				FI	A	8622655	25-12-86
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				FI	C	857004	25-05-92
				GB	A0	8515934	24-07-85
				GB	A	8615800	21-10-86
				HU	A2	420955	29-06-87
				HU	B	1991433	29-01-90
				IE	B	596388	09-03-94
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				JP	A2	62000487	06-01-87
				KR	B1	9309356	28-09-93
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				NO	A	8623504	29-12-86
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				NO	C	1639356	15-08-90
				NZ	A	2165366	28-10-88
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				PT	B	828224	29-07-88
				SU	A3	1581221	23-07-90
				US	A	5041448	20-08-91
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				DE	B2	1695821	23-10-75
				DE	C3	1695821	26-05-76
				ES	A1	349429	01-04-69
FR A	1550912			FR	A	1550912	20-12-68
				FR	M	7559	29-12-69
GB A	1021195			GB	A	1165283	24-09-69
				keine - none - rien			